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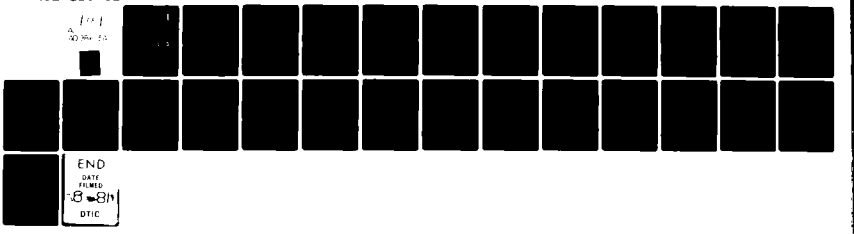

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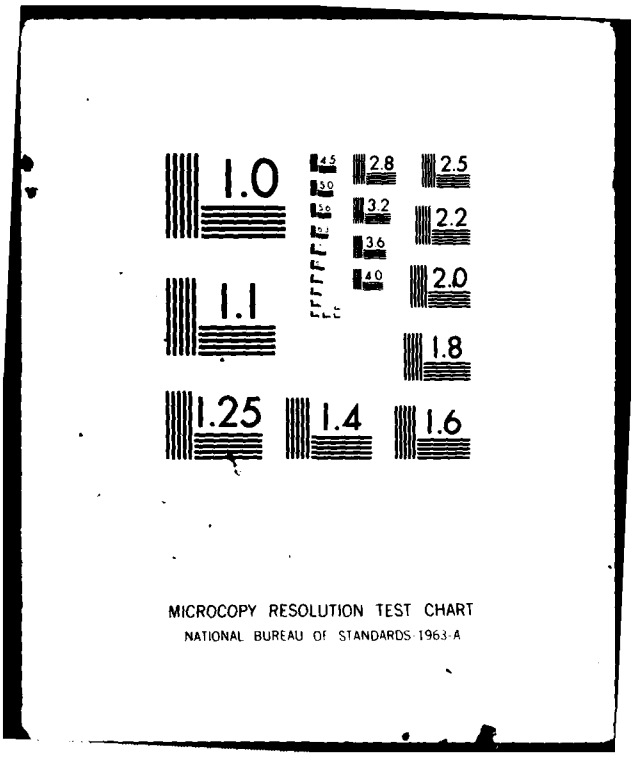

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THE ROLE OF LYSOSMAL ENZYME RELEASE IN CIRCULATORY SHOCK AND CRITICAL ILLNESS. FINAL REPT. 1 APR. 77- 30 JUN. 78. ARR. 80. CONTRACT DAMD17-77-C-7022.

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ROLE OF LYSOSOMAL ENZYME RELEASE IN CIRCULATORY SHOCK AND CRITICAL ILLNESS

FINAL REPORT

Stephen L. Wangensteen, M.D.
and
Paul E. Clinco, M.D.

April 1980
(1 April 1977 - 30 June 1978)

Supported By:

US Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-77-C-7022

Department of Surgery
University of Arizona College of Medicine
Tucson, Arizona 85724

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REPORT DOCUMENTATION PAGE

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1. REPORT NUMBER	2. GOVT ACCESSION NO. / 3. RECIPIENT'S CATALOG NUMBER
4. TITLE *(and Subtitle)*: THE ROLE OF LYSOSOMAL ENZYME RELEASE IN CIRCULATORY SHOCK AND CRITICAL ILLNESS	5. TYPE OF REPORT & PERIOD COVERED: FINAL REPORT: April 1, 1977-June 30, 1978
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): Stephen L. Wangensteen, M.D. and Paul E. Clinco, M.D.	8. CONTRACT OR GRANT NUMBER(s): DAMD 17-77-C-7022
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Department of Surgery, University of Arizona College of Medicine, Tucson, Arizona 85724	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 61102A.3S161102BS05.00.005
11. CONTROLLING OFFICE NAME AND ADDRESS: US Army Medical Research and Development Command, Fort Detrick, Frederick, Maryland 21701	12. REPORT DATE: April, 1980
	13. NUMBER OF PAGES: 20
14. MONITORING AGENCY NAME & ADDRESS *(if different from Controlling Office)*	15. SECURITY CLASS. *(of this report)*: Unclassified
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT *(of this Report)*

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17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

After encountering numerous difficulties in carrying out the intended protocol, emphasis of research was shifted to study another lysosomal membrane stabilizing agent, zinc, and its potential for prevention of stress-induced gastric ulceration.

19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

Lysosomal enzyme release; circulatory shock; zinc as a lysosomal membrane stabilizing agent; gastric ulceration

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

The effect of the lysosomal membrane stabilizing agent, zinc, was studied for potential prevention of stress-induced gastric ulceration. The purpose of the experiment was to examine the relationship between the known membrane actions of zinc and a standardized rat gastric ulcer preparation.

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SUMMARY

Although the final phase of research in this project was intended to study the association of lysosomal enzyme release and the severity of shock in humans, numerous difficulties were encountered in obtaining approval from the Human Subjects Commmittee, obtaining the experimental drug, and adhering to revised restrictions placed on the protocol by the drug supplier. In addition, there were problems in identifying patients and in funding additional personnel to perform the tests necessary to obtain the required data.

Eventually, it was decided to abandon the final phase of the study in the protocol that had been prepared and to emphasize study of the effect of another lysosomal membrane stabilizing agent, zinc. This agent was studied for potential prevention of stress-induced gastric ulceration. Experiments were devised using rats to determine the relationship between the known membrane actions of zinc and a standardized rat gastric ulcer preparation. The primary conclusion that could be drawn from data provided by the studies was that, in the rat, there exists a homeostatic mechanism which regulates the serum zinc in the situation of stress. Treatment with zinc appeared to reduce both the numbers of ulcers and the severity of the ulceration in the rats, although differences were not significant.

FOREWARD

For the protection of human subjects, the investigators have adhered to policies of applicable Federal Law 45CFR46.

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care", as promulgated by the Committee on the Buide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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PREFACE

CLINICAL OBSERVATIONS ON THE EFFECT OF METHYLPREDNISOLONE IN CIRCULATORY SHOCK

A protocol was developed to determine the association of lysosomal enzyme release and severity of shock in humans in states of circulatory shock and conditions of critical illness. Previous studies indicated that release of lysosomal enzymes may be important in the pathogenesis of circulatory shock. The study was aimed at 1) the release of lysosomal enzymes in several forms of clinical shock; and 2) the role of administration of methylprednisolone that may modify the release of lysosomal enzyme. We desired to study patients with the following forms of clinical shock: traumatic shock, hypovolemic shock, septic shock, cardiogenic shock, low output syndrome after open-heart surgery, bowel ischemia shock, and acute hemorrhagic pancreatitis. It was not possible to maintain rigid criteria for admission to the shock study protocol. However, consideration was given to patients who were seriously ill and demonstrated hypotension, failure to respond to fluid administration, high central venous pressure, air hunger, tachycardia, narrow pulse pressure, cold extremities, and peripheral cyanosis. Plasma levels of the lysosomal enzymes, cathepson-D and betaglucuronidase, were determined. Blood pH, pCO_2, pO_2, and arterial venous oxygen differences were studied. Cardiovascular measurements and pulmonary function measurements were also determined.

Patients were to be studied in a prospective, randomized, double-blind fashion. However, a number of difficulties were encountered in carrying out the study. There were delays in obtaining approval from the Human Subjects Committe to conduct the experiments. There were extensive delays in obtaining the drug. When the drug was finally received, further restrictions were placed on the protocol by the drug supplier (the Upjohn Company), subject, in turn, to restrictions levied by the Federal Drug Administration upon it.

The restrictions, along with additional documentation and paperwork requirements, made it not possible, or at least extremely difficult, to obtain the necessary data in patients without the addition of more personnel. This situation occurred at a time when there was no additional funding available.

Another difficulty encountered was that, frequently, a decision had already been made by the responsible physician caring for a critically ill patient as to whether or not steroids should be given before the patient was considered for the study protocol.

Of the patients studied, it was not possible to draw any conclusions from the data collected.

Introduction

In previous years, studies were focused on the elevation of plasma lysosomal enzymes and tissue loss of lysosomal enzymes during various types of circulatory shock. The plasma activities of the lysosomal enzyme Cathepson-D closely paralleled the duration and severity of circulatory shock. Cortical steroids, known to be lysosomal membrane stabilizing agents, were used in several sets of experiments to determine if survival was improved. Although cortical steroids were shown to decrease the tissue loss of lysosomal enzymes from certain visceral organs, they did not significantly prevent plasma elevation of lysosomal enzymes and cortical steroids did not significantly improve survival.

During this final contract period, the effect of another lysosomal membrane stabilizing agent, zinc, was studied for potential prevention of stress-induced gastric ulceration. Many investigators have shown that gastric ulceration in the experimental animal is prevented or reduced by pre-treatment with zinc salts (1, 8, 9). The cellular mechanism of the benefits of zinc, however, have not been studied. Our laboratory has shown previously that zinc stabilizes the plasma membrane of leukocytes, macrophages, and mast cells, and organelle membranes such as that of the lysosome (2, 3). The purpose of the present experiment was to examine the relationship between the known membrane actions of zinc and a standardized rat gastric ulcer preparation.

The Dai-Ogle rat ulcer preparation (5, 6) was selected because the stress of surgical trauma (with associated decrease in serum zinc concentration) is eliminated and no pharmacological manipulations are required. The pathophysiology of pyloric ligation includes: 1) stasis of acid pH secretions, 2) distention of the stomach wall by accumulation of secretions, and 3) mucosal hyperemia secondary to mast cell degranulation (5, 6, 13). Peritoneal and pulmonary mast cells are known to be inhibited by zinc, but gastric mast cells have not been studied. Similarly, volume and

hydrogen ion content of gastric secretions have been shown to be reduced in zinc-treated animals (1).

Grouping of Test Animals:

Two-hundred fifty-gram, female Sprague-Dawley rats were used. A single sex was selected to eliminate potential sex differentiation of the response to stress (both in zinc metabolism and in the severity of ulceration produced). Females were selected because of their superior weight stability over time. Diet and water were provided ad lib. Zinc, as $ZnSo_4$, 0.6 mg/ 100 mg B.W., in solution buffered to pH 6.8 was administered to the treatment group intraperitoneally q 12 h prior to pyloric ligation.

	Control	Sham-op	Dai-Ogle Prep.
Control diet			
Control diet + zinc			

Surgery was performed with Innovar anesthesia because of its minimal stimulus to gastric secretion.

Selection of the Ulcer Model:

a. Serotonin

b. Propionitrile with Cysteamine (12)

These drug-induced ulcer models interfered with the experimental design by introducing new variables. Stress induces mast cell degranulation, as does vagal stimulation, a potent ulcerogen (1).

Serotonin not only induces mast cell degranulation, but is also a major product of the rat mast cell (7). The mechanism of ulceration in the second model is unknown.

c. Restraint

Confinement and lowering of ambient temperature produce ulcers, but the individuality of response leads to a wide basal range of the severity of ulceration, clearly undesirable in a small sample experiment.

d. Shay preparation

The anesthetized animal is subjected to pyloric ligation, wounds closed, and awakened. At sacrifice, two to five hours later, ulcers are repeatably formed. The acute surgical stress, however, will cause shifts in the zinc pool which will mask the "pure" effect of pyloric ligation. This method is briefly described in an article (5) which also mentions two other ulcer models requiring chronic gastric fistulae (with and without excluded pouch) which seemed unduly complex for this experiment.

e. Dai-Ogle preparation

This is a modification of the Shay technique in which a wire loop is loosely placed around the duodenum and brought out through the flanks. The animal is allowed to recover and the pyloric obstruction may then be instituted by pulling the wires at any desired later date. The influence of acute surgical stress and environmental stress is thereby eliminated.

At two hours, most animals will show mucosal petechiae but no ulcers. At five hours, 20% to 50% will demonstrate ulcers, and at eight hours, 80% to 90% will have the desired lesions.

Considerable difficulty was experienced with the rat models, but the Dai-Ogle preparation proved to be the most workable and reproducible.

Data:

A. Zinc homeostasis

1. Serum zinc concentration immediately prior to pyloric lygation
2. Serum zinc concentration immediately prior to sacrifice. In controls, a second serum zinc will be determined at intervals identical to the experimental animals.

B. Gastric morphology

1. Number of ulcers and their location (glandular or rumenal regions of stomach).
2. Number of perforations.
3. Presence or absence of glandular petachiae.

C. Gastric physiology

1. Volume of gastric secretion
2. Titration of gastric acidity. Total secreted hydrogen ion will be computed.
3. Zn^{++} concentration in mucosa. (To be determined by atomic absorption. Specimens will be prepared by washing in deionized water, digestion by HNO_3 and $HClO_4$, resuspension. As far as is possible, the specimen will be collected without the use of metallic instruments (as a guard against contamination of the A.A. determinations).

THE EFFECT OF ZINC ON STRESS-INDUCED GASTRIC ULCERATION

1. Experience with the Model

The experiment underwent three successive trials. The first trial failed because wire of too small a calibre was used for the pyloric ligation, and most of the rats were able to gnaw through it. Substitution of 2-0 for 4-0 stainless steel wire solved this difficulty.

For the second trial, a ligation period of eight hours was selected. Although most of the pylorus-ligated rats survived this length of time, very few, even in the non-zinc-treated group, developed ulcers (although mucosal petechiae were frequently present).

In the third trial, a ligation period of ten hours was selected in order to assure increased ulceration. Ten rats were prepared for each group. All ten controls survived; two sham-operated, zinc-treated animals were slain by cage-mates. Five of each pylorus-ligated group died from the preparation before the ten hours had elapsed and were excluded from analysis. The number of animals in each group, therefore, exceeded the original specifications.

The numeric data was tabulated and fundamental statistics calculated on the Wang 2200 Basic-language computer. The results and the program listings are appended.

2. Data Analysis

Student's t statistic was computed for each group (and each parameter) versus the no-zinc, sham-operated group, following computation of the mean, standard deviation, and standard error for each group.

3. Results

The first table distributes the rats according to the treatment/preparation group.

The second table contains the results of the gastric content analysis at the end of ten hours. The untreated group's mean values differed at a 2.5% significance level (due to the large standard deviation in the no-zinc, Dai-Ogle group). However, in comparing the two sham-operated groups, the zinc-treated animals had a lower mean gastric content at the same significance level. Similarly, in comparing the two Dai-Ogle groups, the zinc-treated animals had a lower mean gastric content than the non-zinc group at a 10% significance level. It may therefore be inferred that zinc treatment is associated with a reduced gastric secretion under the stress test.

The third table demonstrates the changes in gastric pH. In the untreated animals, the stressed group had a significantly reduced pH (3%), while the treated, stressed animals had a negligible, statistically insignificant reduction in pH compared with the untreated controls. In the unstressed animals, zinc treatment was associated with a slight reduction in pH (5 - 10% significance). There was no significant difference between the gastric pH's of the two stressed groups, nor between the two zinc-treated groups. The mean pH of all the manipulated animals was 2.27, lower than that of the controls (~8.5% significance).

The statistics indicated that: a) Zinc treatment in unstressed animals is associated with increased acidity of gastric juice; b) The Dai-Ogle ulcer stress is associated with increased gastric acid output; c) The combination of a) and b) above (zinc + stress) is not associated with a change in gastric acidity; and d) Any manipulation of the animals is associated with an increase in gastric acidity.

Gastric ulcers were identified in the specimens by a mucosal defect with a margin of extravasated blood (½ - 1 mm), the most marked of which was the single perforated ulcer. Defects in the mucosa without the characteristic brown margin were ascribed to forceps trauma during examination. All specimens from both the treated and untreated Dai-Ogle groups showed petechiae, usually

in groups. The ulcers were usually located close to the esophagus, near the lesser curvature. Twelve ulcers were found in the untreated group with a range of 0 to 5 (the latter including the perforation). The treated group had but six ulcers in a range from 0 to 4. These wide ranges are the reason for large standard deviations and a statistically insignificant difference between means of 1.4 and 2.4. If the fact of ulceration and its severity is most important, then the untreated group had 4/5 ulcers with one complication; the treated group has 3/5 ulcers with no complications.

The fifth table displays the serum zinc assay (ng/ml). Among the sham-operated animals, it will be seen that the mean zinc level in the blood was raised by the treatment by approximately 50%, demonstrating the efficacy of the treatment. In the untreated animals, the Dai-Ogle preparation did not significantly alter the mean serum zinc level. The treated animals, however, also did not show a statistically significant difference.

Conclusions that may be drawn are: a) Basal serum zinc levels are not affected by the Dai-Ogle ulcer stress; b) Serum zinc levels elevated by pretreatment revert to normal when the animal is so stressed; c) It follows from a) and b) that, in the rat, there exists a homeostatic mechanism which regulates the serum zinc in the situation of (at least this) stress.

Gastric tissue zinc levels were likewise determined (ng/mg)--as above, by atomic absorption spectrophotometry--and tabulated. In the untreated animals, the Dai-Ogle stress was associated with a slight lowering of the mean tissue zinc level ($3\frac{1}{2}\%$ significance). The treated, stressed group also demonstrated a slight lowering of gastric tissue zinc, but this was not statistically significant. In the stressed animals, zinc treatment was associated with a small but statistically significant elevation of gastric tissue zinc ($<0.1\%$). In the zinc-treated animals, the Dai-Ogle group had a slight, statistically insignificant decrement. From this, it may be concluded that: a) In untreated animals, a gastric

ulcer stress is associated with a decrease in the zinc stored in that organ; b) In ulcer-stressed animals, zinc pretreatment is associated with a maintenance of gastric tissue zinc at the normal level.

The unstressed animals are noted to have insignificantly differing mean gastric tissue zinc levels with regard to zinc pretreatment.

Table 1

ZINC-PEPTIC ULCER RAT STUDY TRIAL # 3

	RAT NUMBER			
	NO ZINC SHAM OP	NO ZINC DAI-OGLE	ZINC SHAM OP	ZINC DAI-OGLE
	001.000	011.000	016.000	024.000
	002.000	012.000	017.000	025.000
	003.000	013.000	018.000	026.000
	004.000	014.000	019.000	027.000
	005.000	015.000	020.000	023.000
	006.000		021.000	
	007.000		022.000	
	008.000		023.000	
	009.000			
	010.000			
MEAN:	5.500	13.000	19.500	26.000
STD. DEV.:	3.027	1.581	2.449	1.581
STD. ERR.:	0.957	0.707	0.866	0.707
STUDENT'S T STAT:		6.301	10.844	17.223
DEG. OF FREEDOM:		13.000	16.000	13.000

VERSUS: NO ZINC, SHAM OP

Distribution of test animals by number according to treatment and stress; program test routine.

Table 2

ZINC-PEPTIC ULCER RAT STUDY TRIAL # 3

GASTRIC CONTENT, ML

NO ZINC SHAM OP	NO ZINC DAI-OGLE	ZINC SHAM OP	ZINC DAI-OGLE
000.697	*MV*	000.366	004.324
000.419	006.524	000.730	001.524
000.444	015.869	000.714	001.569
001.680	019.815	000.920	006.541
001.387	009.195	000.475	001.374
001.212		000.615	
001.113		000.239	
000.262		000.337	
001.439			
001.176			

MV = MISSING VALUE

MEAN:	0.982	10.080	0.549	3.066
STD. DEV.:	0.491	8.131	0.233	2.298
STD. ERR.:	0.155	3.636	0.082	1.028
STUDENT'S T STAT:		2.499	2.462	2.003
DEG. OF FREEDOM:		13.000	16.000	13.000
		VERSUS: NO ZINC, SHAM OP		
Significance level		2.5%	2.5%	5-10%

Student's t statistic: 1.856
Degrees of freedom: 8
versus: Zinc, Dai-Ogle
Significance level 10%

The missing value refers to the one animal in this trial with a free perforation of a gastric ulcer, with emptying of the distended stomach into the peritoneal cavity.

Table 3

ZINC-PEPTIC ULCER RAT STUDY TRIAL # 3
GASTRIC PH

NO ZINC SHAM OP	NO ZINC DAI-OGLE	ZINC SHAM OP	ZINC DAI-OGLE
001.950	002.950	001.750	001.400
002.850	001.750	002.250	001.900
002.800	002.300	001.900	002.050
003.800	001.200	002.400	004.550
002.400	001.400	001.900	002.900
002.900		002.700	
003.400		003.000	
002.700		002.650	
002.600			
002.450			

MEAN:	2.785	1.920	2.318	2.560
STD. DEV.:	0.519	0.711	0.447	1.236
STD. ERR.:	0.164	0.318	0.158	0.553
STUDENT'S T STAT:		2.416	2.044	0.390
DEG. OF FREEDOM:		13.000	16.000	13.000

VERSUS: NO ZINC, SHAM OP

Significance level	3%	5-10%	>20%
Student's t statistic	.996	.421	
Degrees of freedom	8	11	
Significance level	>20%	>20%	

Table 4

Zinc-Peptic Ulcer Rat Study Trial # 3

# of Gastric Ulcers

No Zinc Sham op	No Zinc Dai-Ogle	Zinc Sham op	Zinc Dai-Ogle
0	5	0	4
0	1	0	1
0	2	0	0
0	0	0	1
0	6	0	0
0		0	
0		0	
0		0	
0			
0			
Mean: 0	2.4	0	1.2
Standard Dev.: 0	2.38	0	1.47
Standard Err.:			

Student's t statistic 0.96
Degrees of freedom 8

versus: Zinc, Dai-Ogle

Table 5

ZINC-PEPTIC ULCER RAT STUDY TRIAL # 3
SERUM ZINC

NO ZINC SHAM OP	NO ZINC DAI-OGLE	ZINC SHAM OP	ZINC DAI-OGLE
001.400	001.500	002.000	001.000
001.300	000.900	002.300	001.900
001.300	000.520	001.600	001.200
001.000	000.900	002.200	001.300
001.200	001.500	002.200	000.200
001.000		002.400	
001.200		002.200	
001.100		002.200	
001.300			
001.200			

MEAN:	1.200	1.064	2.137	1.120
STD. DEV.:	0.133	0.427	0.244	0.614
STD. ERR.:	0.042	0.191	0.086	0.274
STUDENT'S T STAT:		0.695	9.744	0.287
DEG. OF FREEDOM:		13.000	16.000	13.000

VERSUS: NO ZINC, SHAM OP

Significance level	>20%	<0.1%	>20%

Student's t statistic	0.086	0.511
Degrees of freedom	8	11
Significance level	>20%	>20%

versus: Zinc, Dai-Ogle

Table 6

ZINC-PEPTIC ULCER RAT STUDY TRIAL # 3

GASTRIC ZINC

NO ZINC SHAM OP	NO ZINC DAI-OGLE	ZINC SHAM OP	ZINC DAI-OGLE
000.099	000.108	000.116	000.097
000.096	000.086	000.115	000.101
000.104	000.099	000.109	000.085
000.121	000.071	000.111	000.127
000.104	000.078	000.093	000.094
000.099		000.104	
000.113		000.104	
000.101		000.104	
000.100			
000.108			

MEAN:	0.104	0.088	0.107	0.100
STD. DEV.:	0.007	0.015	0.007	0.015
STD. ERR.:	0.002	0.006	0.002	0.007
STUDENT'S T STAT:		2.244	0.700	0.496
DEG. OF FREEDOM:		13.000	16.000	13.000
		VERSUS: NO	ZINC, SHAM	OP
Significance level		3½%	>20%	>20%
Student's t statistic		4.0	.068	
Degrees of freedom		8	11	
		versus: Zinc, Dai-Ogle		
Significance level		<0.1%	20%	

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Personnel Support
Contract DAMD 17-77-C-7022

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PUBLICATIONS SUPPORTED BY CONTRACT NO. DAMD17-77-C-7022

No publications were supported by this contract.

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